Other Rheumatologic Conditions

Introduction

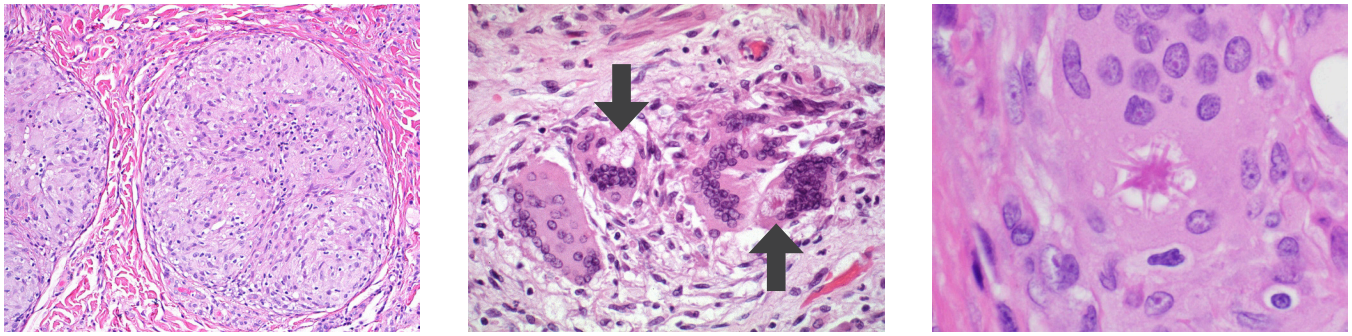
These conditions are an assortment of unrelated rheumatologic diseases. Some of them happen to start with "S," though don't draw any thematic connection based on the alliteration. These are distinct diseases that are autoimmune in nature and aren't large enough to demand their own lessons, but aren't small enough to be ignored. Much of these diseases for the basic sciences comes down to pathognomonic presentation and radiographic or histologic association.

We cover sarcoidosis, scleroderma, Sjogren's syndrome, mixed connective tissue, and antiphospholipid antibody syndrome, one at a time.

Sarcoidosis

Sarcoidosis (also called just sarcoid) is immune-mediated and is based on the formation of **macrophage-induced noncaseating granulomas**. These granulomas can get into any tissue, anywhere.

Noncaseating (non-necrotic) granulomas are identifiable by the typical granulomatous appearance (the granuloma) but with nuclei visible in the granuloma. There will be the pink stuff (granuloma) surrounded by blue dots (leukocytes, macrophages) that you expect in granulomas, except that because it is noncaseating, which means not necrosis, there will be blue dots in the pink stuff, too, representing living cells within the granuloma. You must be able to recognize the granuloma (Figure 4.1a), and bonus if there are the additional histologic findings: Schaumann bodies and asteroid bodies, which may exist within the granuloma.



(a) (b) (c)

Figure 4.1: Histologic Sarcoidosis
(a) granulomas are clustered aggregates of histiocytes and giant cells. In sarcoidosis, the granulomas usually lack necrosis (i.e.—they are non-necrotizing/non-caseating) and have little or no associated lymphocytes, neutrophils, or other inflammatory cell. (b) A higher power image of multinucleated giant cells (fused macrophages) as well as demonstration of the asteroid body—stellate inclusions—as well as a Schaumann body (though the crystal formation is blurred). (c) A higher power view of the asteroid body in the cell in the center of the slide.

Macrophages make the granuloma. We discussed this in detail in the development of the "prison cell" for tuberculosis in Microbiology: Bacteria #14: *Mycobacteria.* There, we described a Th1-mediated immune response. An initial phagocyte engulfs an antigen, and releases IL-2. IL-2 induces Th0 CD4 cells to become Th1. Th1 CD4 cells release IFN-γ, which activates macrophages. Macrophages get more and more activated, release more IL-2, make more Th1, which releases more IFN-γ. This causes the macrophages to get larger, eventually fuse into multinucleated giant cells, and eventually die, forming the granuloma. This same process is thought to happen in sarcoidosis, only the macrophages don't die and we don't know what antigen the original macrophage is responding do.

Macrophages make the granuloma, but macrophages also make angiotensin-converting enzyme (ACE) and 1α-hydroxylase. If measured (there is no clinical utility in doing so) **serum ACE levels** will be elevated, though hypertension is not part of the disease. **1α-hydroxylase** converts 25-OH-VitD into **1,25-OH-VitD**. The kidneys normally do this, activating 1,25-OH-VitD. Activated VitD causes increased calcium absorption. This can lead to mild hypercalcemia and modest hypercalciuria, and can precipitate calcium stones. Neither ACE nor 1,25-OH-VitD levels are useful clinically to diagnose sarcoid; however, some of the pathologic findings can be tied back to these associations.

Pulmonary sarcoid is the classic disease, presenting with **bilateral hilar lymphadenopathy—**the nodes of the lung are huge. Separately, and not necessarily in all cases, sarcoid can result in **diffuse parenchymal lung disease** (previously known as interstitial lung disease), presenting with **ground-glass opacities on CT** scan **and a restrictive lung disease** on pulmonary function tests. Hypoxemia predominates in a restrictive lung disease.

Extrapulmonary sarcoidosis is possible, and any one person's disease is unlike another's. Sarcoid granulomas can be found in and cause dysfunction in any organ. Granulomas in the heart can cause **heart block** and **bradyarrhythmias**. Granulomas in the nerves of the face can lead to Bell's palsy. Granulomas in the skin can cause a rash called **lupus pernio** (a bumpy, malar-appearing rash that does not spare nasolabial folds). Uveitis, inflammatory arthritis, and erythema nodosum are also associated with the disease.

The classic presentation is a **young African-American female** with **cough and dyspnea** and **hilar lymphadenopathy** found on X-ray.

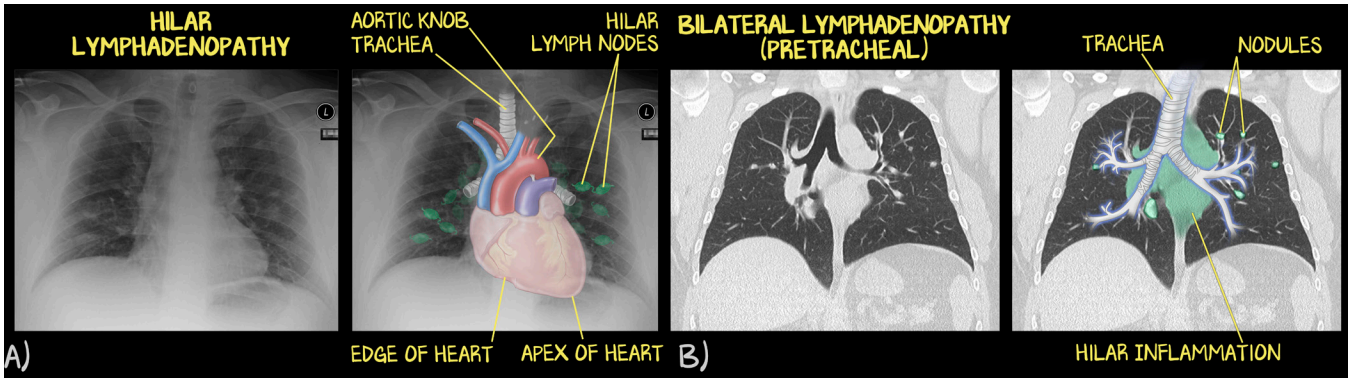


Figure 4.2: Sarcoidosis
(a) X-ray showing bilateral hilar lymphadenopathy and multiple pulmonary nodules. (b) The first of two nearby coronal slices of a chest CT, as viewed on lung window mode, demonstrates bilateral hilar lymphadenopathy, patent airway, and pretracheal lymphadenopathy. Lymphadenopathy is seen as "white stuff where there should be grey." (c) Shows that the peripheral nodules, which appeared randomly scattered, are connected to the central lymphadenopathy. Both scans show the lung parenchyma to be unaffected. (d) Patient with sarcoidosis who is exhibiting erythema nodosum, which is a symptom of sarcoidosis but not pathognomonic for the disease.

Sarcoid flares are treated with **steroids**. Lung disease is treated with oxygen.

Scleroderma

Scleroderma is a **noninflammatory** autoimmune disease that results in **collagen deposition** where collagen shouldn't be. Collagen is the material of scar tissue. Scar tissue doesn't do whatever the tissue it replaces did. That means as more collagen replaces normal tissue, there will be a progressive loss of function that the lost tissue did. Medical science has not elucidated the pathogenesis of this disease other than to note that there is endothelial injury and activation of fibroblasts that lay down

collagen, and that collagen is perivascular to start. Fibroblasts are supposed to be the end product of inflammation—neutrophils first to gobble a pathogen, die in place while summoning macrophages who clear the field, so fibroblasts can lay down collagen. But in scleroderma, despite there being fibrosis and collagen deposition, there has not been evidence of the acute inflammation that happens first. And so, while many theories exist as to the pathogenesis, this condition should be considered **noninflammatory, idiopathic,** and **collagen deposition**. When collagen is seen in tissue at the histologic level, we call it fibrosis. Scleroderma results in **fibrosis** of the **blood vessels,** a noninflammatory vasculopathy (not vasculitis), and in fibrosis of visceral organs. Which organs are affected determines the type. In all forms of scleroderma there is **fibrosis of the skin**. Fibrosis means hardening. That hardening is because healthy tissue is replaced by collagen.

There are two major forms of scleroderma. **Diffuse cutaneous systemic sclerosis** (dcSSc) is the bad form, where the collagen deposition happens in all organs, visceral and skin. It was formerly known as systemic sclerosis or simply scleroderma. **Limited cutaneous systemic sclerosis** (lcSSc) is a more benign variant of scleroderma that affects only the skin of the hands, arms, and face. Some forms of lcSSc present with CREST syndrome. For simplicity, you should learn lcSSc is CREST, and dcSSc is CREST + more fibrosis.

LABEL		DESCRIPTION
C	Calcinosis	Calcium deposits, nodules
R	Raynaud's	Vasospasm when exposed to cold
E	Esophageal dysmotility	Unrelenting GERD from a **decreased LES pressure**, hypomotility
S	Sclerodactyly	Localized thickening and tightness of the skin of the digits
T	Telangiectasias	Skin marks, usually red to purple, nonpalpable

Table 4.1: CREST Syndrome

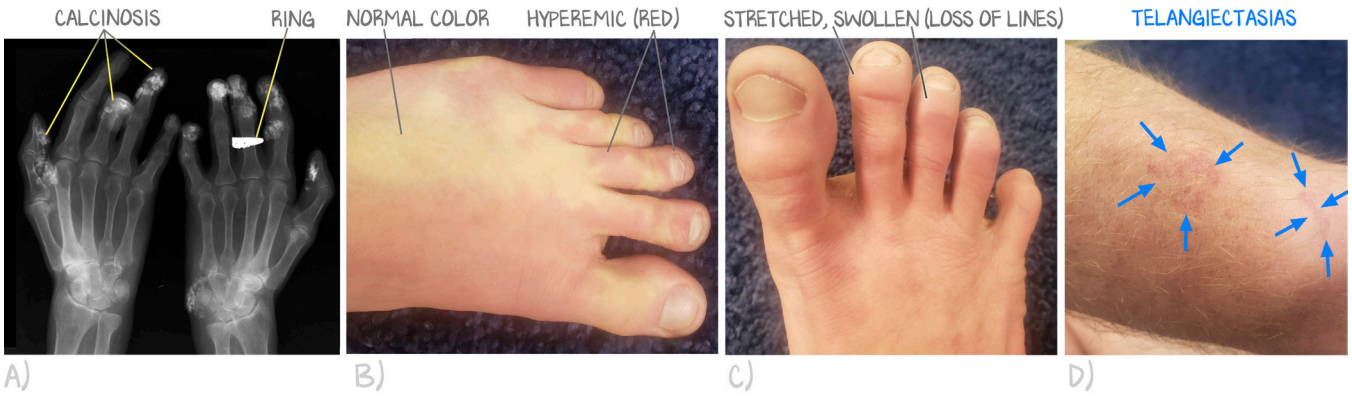


Figure 4.3: CREST Syndrome
(a) Calcinosis can be easily detected on x-ray and is often on the ends of affected digits. The calcinosis can be anywhere, however, as is seen in the bottom of the x-ray, in the patient's right hand (right side of image). (b) Raynaud's syndrome is vasoconstriction that leads to whitening or purpling of the skin (not shown). When the episode terminates, the skin becomes hyperemic (red) before returning to its normal color. There is no example available for esophageal motility. (c) Sclerodactyly is a localized thickening and tightness of the skin of the fingers or toes. It stretches the skin, resulting in the loss of skin folds. It can become so severe that it bends the digits or results in ulceration. This example shows only the loss of skin folds and nail changes. The middle toe and the proximal phalange are the least affected. (d) Although the blood vessels are not as prominent as in some other cases, the purply pink splotches are telangiectasias. The arrows mark the outer borders, as they are not always easy to see.

Lungs. DcSSc gets pulmonary involvement with **interstitial fibrosis**, leading to hypoxemia; subsequent pulmonary hypertension may develop. LcSSc can get **pulmonary hypertension** without any lung lesions—fibrosis of the pulmonary artery leads to pulmonary hypertension.

Kidneys. DcSSc can also present with **scleroderma renal crisis** (oliguria, thrombocytopenia, microangiopathic hemolytic anemia, and a precipitous rise in creatinine) associated with malignant hypertension. The arterial vessels are sclerosed. The hypertension is what causes the damage and subsequent thrombosis in the vessels infarcts the kidneys. This can be **precipitated by steroids** (this is not an inflammatory disease; DO NOT USE STEROIDS to treat it) and must be treated with **ACE inhibitors** (even though the creatinine is very high). LcSSc never affects the kidneys.

Antibodies. DcSSc is diagnosed by an antiscleroderma antibody, **anti-Scl-70,** which is antibody against **topoisomerase 1** as well as **RNA polymerase 3 antibodies**. LcSSc, CREST syndrome, is diagnosed with an **anticentromere** antibody.

There is **no treatment** for either type of scleroderma. The only thing we can do is symptomatic relief of reflux symptoms—GERD with PPIs, Raynaud's with calcium-channel blockers, and pulmonary hypertension with pulmonary hypertension meds. Because there is no antibody or immune cell at play, steroids do not work, nor do any disease-modifying agents, nor do any biologics.

LCSSC (CREST)		DSSSC (SYSTEMIC SCLEROSIS)
Fingers and toes	Skin Fibrosis	Face, fibrosis past elbows
GERD	GI	GERD
Pulm HTN without lung lesion	Lung	Fibrosis, then pulm HTN
None	Kidneys	Scleroderma renal crisis
None	Heart	Block, pericarditis, myocarditis
Anticentromere	Antibodies	Topoisomerase 1 RNA polymerase 3 antibody

Table 4.2: LcSSc vs. DsSSc

Mixed Connective Tissue Disease (MCTD)

MCTD is a difficult disease, both in life and on the test. MCTD is the diagnosis when a patient has features of multiple rheumatologic diseases, but fails to meet the criteria for just one in their entirety. This poses a diagnostic conundrum, because you learn the diseases as discrete silos, without overlap. MCTD displays features of **lupus, scleroderma**, and/or **polymyositis**. If you see features of multiple diseases, choose mixed connective tissue disease. The test question will either be ALL ONE disease or AN OBVIOUS MIX. In particular you should see **Raynaud's** or puffy hands, the **prominence of hand arthritis and erosions** but without destruction of the joints, and **pulmonary hypertension**. MCTD also has the **absence of renal disease** and the **absence of pulmonary fibrosis** (the pulmonary hypertension is not from hypoxemic lung disease).

The real thing to know about MCTD is to be able to spot it as "not another rheum disease" and remember to get an **anti-U1 RNP antibody** (also called a speckled ANA).

Sjogren's Syndrome

This is a disorder of autoimmune **destruction of exocrine glands** (especially lacrimal and salivary). There will be a **lymphocytic infiltration** of the salivary glands, leading to dysfunction of the glandular (fluid-secreting) cells. This happens predominantly in **women** in their **40s–60s**. Destruction of the salivary glands (no salivation) and destruction of the tear ducts (no tears) leads to **dry eyes and dry mouth** (called keratoconjunctivitis sicca and xerostomia, respectively). Dry eyes present with the sensation of dirt or rocks in the eye. Dry mouth presents with the inability to chew or swallow dry foods. In addition to the classic chronic complaints of dry mouth and dry eyes, there can also be an acute presentation of parotitis (parotid-itis) called **autoimmune sialadenitis**, presenting with **bilateral painful parotid enlargement** but without an obstructing stone. There is no treating the cause of the disease, but you can supply tears and saliva (artificially) to prevent the symptoms and complications.

Complications of Sjogren's can result. From the lack of saliva, the dry mouth puts them at risk for **cavities** (dental caries) and infections (thrush). From long-term inflammation of the glands, nearby MALT tissue will be constantly stimulated, just as with *H. pylori* infection in the stomach. This ongoing inflammation leads to a **MALT lymphoma** (a B-cell lymphoma). This will present as a **unilateral painless parotid swelling**, frustrating learners because there are two presentations of parotid within the same illness script. The painless and unilateral parotid presentation is cancer. The painful bilateral parotid presentation of Sjogren's is inflammatory.

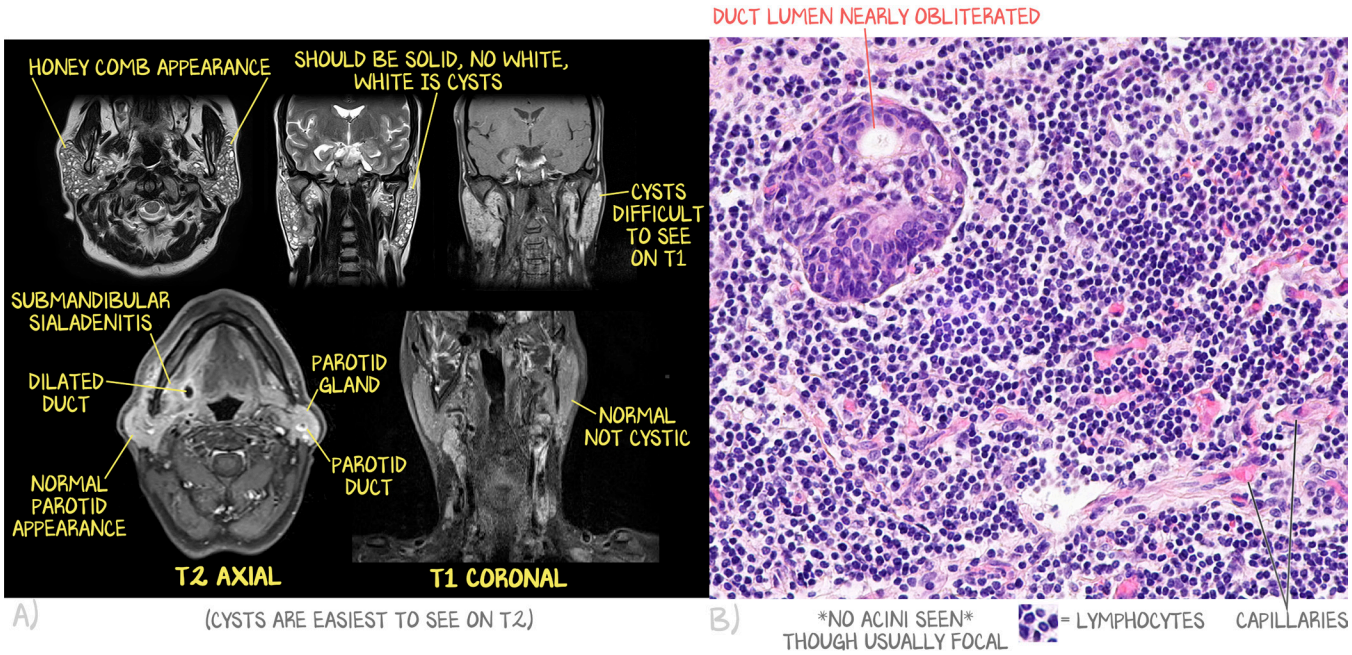


Figure 4.4: Sjogren's
(a) Two separate cases are combined to demonstrate the radiological appearance of the effects of Sjogren's on the parotid gland. The bottom row shows a case of submandibular sialadenitis, a blockage of the submandibular gland's duct by a stone. The parotids are unaffected. The parotids appear continuous, not cystic, and are of one color and texture. That is true both when T1 weighted (left) and T2 weighted (right). The top row shows an axial T2-weighted MRI, a coronal T2-weighted MRI, and a coronal T1-weighted MRI to demonstrate the "honeycomb appearance"—the multiple cysts the parotid gland has become. (b) High-power light microscopy shows a near obliterated duct, and everywhere there should be acini, there are lymphocytes instead.

Sjogren's is associated with screening antibodies ANA and RF, but is diagnosed with antibodies to **ribonucleoprotein** known as SS-A (**anti-Ro**) and SS-B (**anti-La**). The "SS" stands for Sicca Syndrome, the other name for Sjogren's, and so is unlikely to be the named antigen on your licensing exam.

Sjogren's is so common in conjunction with other diseases that if Sjogren's is diagnosed, **an aggressive search for other rheumatologic conditions** is indicated. Sjogren's itself is eyes and mouth, but there is also often Raynaud's and arthritis because Sjogren's is part of other rheumatologic diseases.

Ancillary tests to confirm the absence of tearing (Schirmer wet paper test) and absence of salivation (nuclear uptake of radionucleotide is reduced) may be performed, but are often unnecessary as symptoms and antibodies are sufficient to make the diagnosis.

Antiphospholipid Antibody Syndrome (APLA)

APLA is an antibody-mediated **hypercoagulable** state that results in **arterial and venous thrombosis**. APLA is caused by . . . you guessed it, antibodies to phospholipid. In vivo, in a living person, this causes thrombosis. It is associated with lupus, though can exist as an independent disease. In vitro, in the lab, as we will see later, APLA is diagnosed as being an anticoagulant. Anticoagulant in the lab, procoagulant in the patient.

The presence of both arterial and venous thrombosis is an obvious presentation. But the disease gets hard in the basic sciences because these antibodies are tricky for learners. Any one of these antibodies confirms the diagnosis, not all three are always present, and then there is something else to know about each one. The **anticardiolipin** antibody causes **falsely elevated VDRL/RPR** even in the absence of a syphilitic infection (the antibodies cause a false positive on the lab test), so a positive syphilis testing in someone without risk factors and who is clotting should be assessed for anticardiolipin antibodies and APLA. The **lupus anticoagulant** (called that because it is an anticoagulant in the laboratory) is what **causes thrombosis to occur** (so is a procoagulant). It is also present in more than just lupus, as APLA can exist without lupus. More on this in the next paragraph. The antibody that no one ever remembers is **anti-β2 glycoprotein**. It also does not have any cool association with screwing up labs. It is also the one learners forget.

ANTIBODY	TRICKSY
Anticardiolipin	False elevation of RPR and VDRL
Lupus anticoagulant	Anticoagulant in vitro Procoagulant in vivo
β2-glycoprotein	The one everyone forgets.

Table 4.3: Antiphospholipid Antibodies

A **dilute Russell's viper venom test** screens for the lupus anticoagulant, an antibody to phospholipid, and is where the antibody gets its name. A sample of the patient's blood is diluted down and added to a mixture of phospholipids and venom. The presence of clotting factors from the plasma and the mixture should cause a clot to form. When an antiphospholipid antibody (the "anticoagulant") is present, it binds the phospholipids, so no clot forms, manifesting as a prolonged bleeding time. If the patient's plasma were deficient of a clotting factor, we would have the same result. So, an equal mixture of patient plasma is added to normal plasma (a mixing study). The normal plasma has sufficient clotting factors to reverse a clotting factor deficiency. The normal plasma has clotting factors, but the antiphospholipid antibody still prevents clotting. Finally, **confirmatory Russell's viper venom** testing is performed by dousing the sample with phospholipids, which causes the concentration of phospholipids to exceed the antibodies, and a clot forms. Dilution in the initial step is necessary to ensure that there is sufficient phospholipid if there is no antibody, but insufficient phospholipid so that the presence of antibody can

prevent clotting. Increasing the concentration of phospholipid in the confirmatory step is to ensure the patient's serum could clot. Of course, you do a mixing study usually for a patient with bleeding and an elevated PT or PTT. In APLA, you do a mixing study because a patient has **clotting** despite an elevated PT or PTT.

This is the only disease that will present with both arterial and venous thrombosis. Treatment is with **warfarin** if not trying to get pregnant, and with **aspirin** (arterial thrombosis) and **LMWH** (venous thrombosis) if trying to get pregnant.

Citations

Figures 4.1a, 4.1c: Courtesy of Jerad M. Gardner, MD.

Figure 4.1b: Originating from the University of Alabama at Birmingham, Department of Pathology PEIR Digital Library at http://peir.net pursuant to a license grant by the UAB Research Foundation.